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Titanium tetrafluoride: An efficient Lewis acid and fluorinating agent for stereoselective synthesis of 4-fluorotetrahydropyran

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ABSTRACT

Titanium tetrafluoride can efficiently be used for strereoselective synthesis of 4-fluorotetrahydropyrans via Prins cyclization in good yields. The method is general and can be used for aldehydes as well as ketones.

1. Introduction

Selective introduction of fluorine atoms into organic molecules is prevalent in the fields of pharmacology, agrochemical and functionalized materials because of the unique biological and physical properties of the resulting compounds [1–4]. Several 3-fluoroalkylamines [5] and vinyl fluorides [6] have been shown to be irreversible inhibitors of certain enzymes. Similarly deoxyfluorosugars have been used to probe the mechanism of action of various enzymes [7]. Recently, the synthesis of fluorinated sugars and related heterocycles is gaining importance due to their varied biological activity [8–12]. The synthesis of substituted tetrahydropyran unit is important in organic chemistry because of its presence in many biologically active natural products [13–20]. Although there are many methods for the synthesis of halogenated [21–25], acetylated [26–28], arylated [29,30], hydroxylated [31–33] and amidated [34,35] tetrahydropyran, methods for the synthesis of fluorinated tetrahydropyran are limited [25,26,36–39]. Prins cyclization is generally used for the construction of tetrahydropyran unit [40,41]. Most of the existing methods for the synthesis of fluorinated tetrahydropyran suffers serious drawback such as multistep synthesis [25], low yield [25,26,38], non-selective [36] and formation of hydroxylated by-products [39]. Fuchigami and coworkers have reported an efficient method for the synthesis of 4-fluorotetrahydropyrans, but it fails to give good yields with ketones [37]. Therefore, there is a need for development of new and efficient methodology for the synthesis of fluorinated tetrahydropyran. Titanium tetrafluoride has long been used as a Lewis acid in addition [42–47], and ring-opening reactions [48]. The use of titanium tetrafluoride both as a Lewis acid and fluorinating agent has not been reported. Recently, we have reported one-pot three-component synthesis of 4-aryltetrahydropyran via Prins–Friedel–Crafts reaction mediated by boron trifluoride etherate [29]. In this paper, we wish to disclose a methodology for the stereoselective synthesis of 4-fluorotetrahydropyran via Prins cyclization reaction using titanium tetrafluoride as Lewis acid as well as fluorinating agent.

2. Results and discussion

In continuation of our interest in fluorine chemistry [49], we were in search of a high yielding, efficient method for the synthesis of fluorinated tetrahydropyran and considered titanium tetrafluoride as a reagent of choice. Initially benzaldehyde was reacted with homoallyl alcohol in the presence of titanium tetrafluoride in dichloromethane at room temperature. The product 4-fluoro-2-phenyltetrahydropyran was obtained in 82% yield within 3 h. The reaction is stereoselective and all substituents are in *cis* position. The reaction is generalized as shown in Scheme 1.

To prove its general applicability, varieties of aliphatic and aromatic aldehydes were examined and it was observed that all types of aldehydes give good yields with high diastereoselectivity (Table 1). The substituents on the aromatic ring have some effect on the reactivity of the aldehydes. Electron-withdrawing sub-

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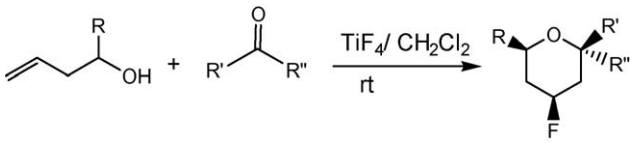


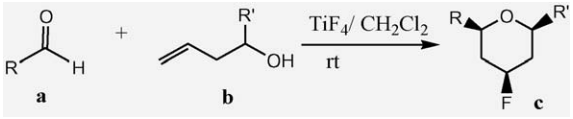
Scheme 1. Synthesis of 4-fluorotetrahydropyran.

stituents reacted faster with better yields than the simple aromatic and electron donating groups on the ring. The conformations of the di- and tri-substituted tetrahydropyrans thus obtained are of chair form and all the substituents are in equatorial position. This was confirmed by NOE experiment and single crystal X-ray analysis (see Appendix B) [50].

The reactivity of acyclic and cyclic ketones was also studied. They were comparatively unreactive and gave moderate yields. Cyclic ketones afforded spiro compounds (Table 2). Thus, the reaction of acetone gave 4-fluoro-2,2-dimethyl-6-(4-nitrophenyl)-tetrahydropyran **18c** in 65% yield, whereas cyclohexanone and cyclododecanone gave spirocyclic compounds **19c** and **20c** in 70% and 50% yields, respectively. Cyclic diketone such as cyclohexane-1,4-dione gave spirocyclic compound **21c** in 55% yield.

The mechanism of the reaction can be explained as follows. Titanium tetrafluoride acts as a Lewis acid and activate the aldehydes for nucleophilic attack by homoallyl alcohol **22** leading to the intermediate **23** and a fluoride ion (Scheme 2). The intermediate **23** forms oxocarbenium ion **24**, which after cyclization gives tetrahydropyranyl cation **25**. The intermediate tetrahydropyranyl cation **25** forms the most stable chair-like

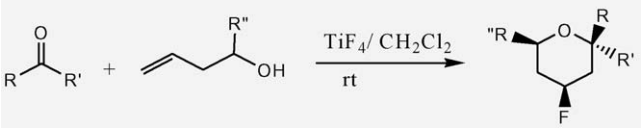
Table 1
Prins cyclization of aldehydes with homoallylic alcohols with TiF_4.

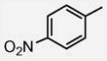
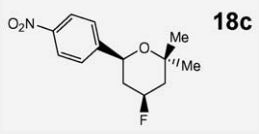
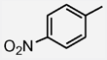
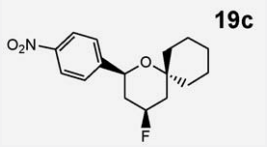
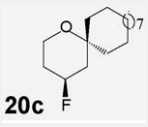
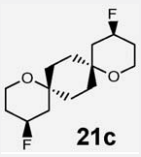


Entry	Aldehyde (a) *R*=	Alcohol (b) *R′*=	Time/h	Product (c)	(%) Yield[a]
1	C_6H_5	H	3	**1c**	82
2	*p*-MeC_6H_4	H	3	**2c**	84
3	*p*-FC_6H_4	H	3	**3c**	85
4	*p*-ClC_6H_4	H	3	**4c**	86
5	*o*-ClC_6H_4	H	3	**5c**	85
6	*m*-BrC_6H_4	H	3	**6c**	90
7	*o*-$NO_2C_6H_4$	H	2.5	**7c**	89
8	*m*-$NO_2C_6H_4$	H	2.5	**8c**	92
9	*p*-$CF_3C_6H_4$	H	3	**9c**	90
10	*p*-$MeSC_6H_4$	H	4	**10c**	85
11	$C_6H_5C_2H_4$	H	4	**11c**	87
12	C_6H_5	*p*-$NO_2C_6H_4$	4	**12c**	80
13	*p* -$MeO_2CC_6H_5$	H	3	**13c**	90
14	*p*-$PhSO_3C_6H_5$	H	2.5	**14c**	92
15	C_6H_{13}	*p*-$NO_2C_6H_5$	3	**15c**	80
16	C_3H_7	*p*-$MeO_2CC_6H_5$	3	**16c**	80
17	$C_{10}H_{21}$	H	3	**17c**	85

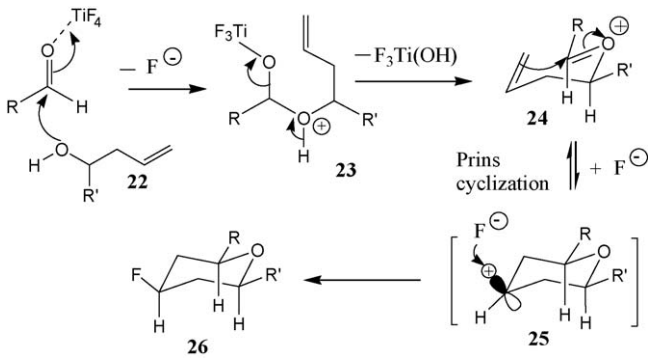
[a] Yield refers to isolated yield. All compounds are characterised by ^1H, ^{13}C, ^{19}F NMR, IR spectroscopy.

Table 2
Prins cyclization of Ketones with homoallylic alcohols with TiF_4.



Entry	Ketone	Alcohol *R″*	Time (h)	Product	Yield[a] (%)
18			5	 **18c**	65
19			5	 **19c**	70
20		H	6	 **20c**	50
21		H	6	 **21c**	55

[a] Yield refers to isolated yield. All compounds are characterised by ^1H, ^{13}C, ^{19}F NMR, IR spectroscopy.



Scheme 2. Mechanism of the reaction.

transition state, placing both R and R′ in the equatorial positions. The nucleophilic attack by fluoride ion occurs from the equatorial position exclusively to give most stable 4-fluorotetrahydropyran **26**.

3. Conclusion

In summary, we have demonstrated that titanium tetrafluoride can be used as a Lewis acid as well as fluorinating agent for the synthesis of fluorotetrahydropyran via Prins cyclization reaction in good to excellent yields. In contrast to existing methods in the literatures, the advantages of this method are: the high yields in case of aromatic and aliphatic aldehydes, high stereoselectivity, short reaction time, one-pot and non-formation of side products. The method can be extended to cyclic ketones for the synthesis of spirocyclic compounds in good yields.

4. Experimental

4.1. General remarks

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian AS 400 (400 MHz) spectrometer using TMS as internal standard. ^{13}C and ^{19}F NMR spectra were obtained on Varian AS 400 operating at 100 MHz and 376 MHz respectively. IR spectra were recorded on Nicolet Impact 410 FT-IR spectrometer. Elemental analysis was performed on Perkin Elmer 2400 Series II CHNS analyzer.

4.1.1. General procedure for the synthesis of 4-fluoro-2-phenyltetrahydropyran (1c)

To a mixture of benzaldehyde (200 mg, 1.88 mmol) and TiF_4 (234 mg, 1.88 mmol) in dry CH_2Cl_2 (2 mL) was added 3-buten-1-ol (163 mg, 2.26 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 2.5 h. After completion of the reaction the solvent was removed by rotary evaporator. The resultant residue was extracted with ethyl acetate (2 × 15 mL) and the combined organic layer was washed with brine and water, dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel) using ethyl acetate and hexane (EtOAc:hexane, 1:4) as eluent to give 278 mg (82%) of **1c** as colorless oil.

4.1.2. 4-Fluoro-2-phenyltetrahydropyran (1c)

(82%) Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70–1.90 (m, 2 H), 2.00–2.12 (1 H, m), 2.30–2.34 (1 H, m), 3.55 (1 H, dt, J = 12.4, 1.20 Hz), 4.17–4.22 (1 H, m), 4.30 (1 H, dd, J = 11.2, 2.0 Hz), 4.68–4.90 (1 H, m), 7.25–7.35 (5 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.2 (d, J = 17.5 Hz), 40.7 (d, J = 16.7 Hz), 65.7 (d, J = 12.2 Hz), 78.1 (d, J = 10.6 Hz), 89.6 (d, J = 176.2 Hz), 126.1, 128.1, 128.7, 141.5. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −7.95 (m, –CF–). IR: 2959, 2854, 1375, 1160, 1081, 1040, 981, 757, 699, 588 cm^{-1}. Anal. Calcd for $C_{11}H_{13}FO$: C, 73.31; H, 7.27. Found: C, 73.38; H, 7.21.

4.1.3. 4-Fluoro-2-p-tolyltetrahydropyran (2c)

(84%) Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71–1.90 (m, 2 H), 2.07–2.13 (1 H, m,), 2.27–2.32 (1 H, m), 2.33 (3 H, s), 3.55 (1 H, tt, J = 14.0, 2.0 Hz), 4.16–4.22 (1 H, m), 4.27 (1 H, dd, J = 11.6, 2.0 Hz), 4.69–4.89 (1 H, m), 7.15 (2 H, d, J = 8.0 Hz), 7.23 (2 H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.1 (d, J = 17.5 Hz), 40.6 (d, J = 16.8 Hz), 65.5 (d, J = 11.4 Hz), 77.0 (d, J = 10.6 Hz), 89.4 (d, J = 176.2 Hz), 115.5 (d, J = 21.4 Hz), 127.8 (d, J = 7.6 Hz), 137.3, 162.5 (d, J = 244.8 Hz). ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −7.88 (m, –CF–). IR: 2959, 2855, 1372, 1160, 1082, 1040, 981, 814, 596 cm^{-1}. Anal. Calcd for $C_{12}H_{15}FO$: C, 74.20; H, 7.78. Found: C, 74.25; H, 7.81.

4.1.4. 4-Fluoro-2-(4-fluorophenyl)-tetrahydropyran (3c)

(85%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.64–1.90 (2 H, m), 2.10–2.15 (1 H, m), 2.27–2.35 (1 H, m), 3.56 (1 H, tt, J = 12.4, 1.6 Hz), 4.17–4.24 (1 H, m), 4.30 (1 H, dd, J = 11.2, 2.0 Hz), 4.71–4.91 (1 H, m), 7.00–7.10 (2 H, m), 7.31–7.34 (2 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.1 (d, J = 17.5 Hz), 40.8 (d, J = 16.7 Hz), 65.6 (d, J = 12.2 Hz), 77.1 (d, J = 10.6 Hz), 89.6 (d, J = 175.4 Hz), 115.5 (d, J = 21.4 Hz), 127.8 (d, J = 7.6 Hz), 137.3, 162.5 (d, J = 244.8 Hz). ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.30 (m, –CF–), 47.14. IR: 2961, 2855, 1605, 1514, 1373, 1225, 1157, 1082, 1040, 982, 834, 595 cm^{-1}. Anal. Calcd for $C_{11}H_{12}F_2O$: C, 66.66; H, 6.10. Found: C, 66.71; H, 6.12.

4.1.5. 4-Fluoro-2-(4-chlorophenyl)-tetrahydropyran (4c)

(86%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71 (1 H, p, J = 10.0 Hz), 1.85 (1 H, dp, J = 11.2, 4.8 Hz), 2.10–2.17 (1 H, m), 2.28–2.37 (1 H, m), 3.56 (1 H, tt, J = 12.4, 1.6 Hz), 4.18–4.24 (1 H, m), 4.30 (1 H, dd, J = 11.6, 2.0 Hz), 4.72–4.92 (1 H, m), 7.27–7.35 (4 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.1 (d, J = 18.3 Hz), 40.6 (d, J = 17.6 Hz), 65.7 (d, J = 12.2 Hz), 77.0 (d, J = 10.6 Hz), 89.4 (d, J = 176.2 Hz), 127.4, 128.8, 133.7, 140.0. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.30 (m, –CF–). IR: 2961, 2855, 1494, 1371, 1160, 1084, 1041, 982, 825, 589 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClFO$: C, 61.55; H, 5.63. Found: C, 61.59; H, 5.65.

4.1.6. 4-Fluoro-2-(2-chlorophenyl)-tetrahydropyran (5c)

(85%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.61 (1 H, m), 1.80–1.93 (1 H, m), 2.11–2.17 (1 H, m), 2.45–2.51 (1 H, m), 3.60 (1 H, tt, J = 14.0, 1.6 Hz), 4.20–4.26 (1 H, m), 4.70 (1 H, dd, J = 11.2, 2.0 Hz), 4.75–4.95 (1 H, m), 7.20–7.26 (1 H, m), 7.28–7.35 (2 H, m), 7.55–7.57 (1 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.1 (d, J = 18.3 Hz), 39.3 (d, J = 16.7 Hz), 65.6 (d, J = 11.4 Hz), 74.6 (d, J = 12.2 Hz), 89.2 (d, J = 176.2 Hz), 127.3, 127.4, 128.9, 129.5, 131.5, 139.2. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.20 (m, –CF–). IR: 2963, 2856, 1445, 1372, 1159, 1083, 1039, 982, 755, 593 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClFO$: C, 61.55; H, 5.63. Found: C, 61.57; H, 5.68.

4.1.7. 4-Fluoro-2-(3-bromophenyl)-tetrahydropyran (6c)

(90%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.64–1.75 (1 H, m), 1.78–1.90 (1 H, m), 2.10–2.14 (1 H, m), 2.28–2.30 (1 H, m), 3.54 (1 H, tt, J = 12.4, 1.6 Hz), 4.17–4.23 (1 H, m), 4.28 (1 H, dd, J = 11.6, 2.0 Hz), 4.70–4.90 (1 H, m), 7.20–7.27 (2 H, m), 7.40–7.43 (2 H, m), 7.52 (1 H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 17.6 Hz), 40.7 (d, J = 12.2 Hz), 65.6 (d, J = 12.2 Hz), 77.0 (d, J = 10.0 Hz), 89.2 (d, J = 176.2 Hz), 122.8, 124.6, 129.2, 130.2, 131.0, 143.7. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.30 (m, –CF–). IR: 2960, 2854, 1568, 1427, 1369, 1159, 1082, 1041, 983, 783, 695, 599 cm^{-1}. Anal. Calcd for $C_{11}H_{12}BrFO$: C, 50.99; H, 4.67. Found: C, 51.05; H, 4.70.

*4.1.8. 4-Fluoro-2-(2-nitrophenyl)-tetrahydropyran (**7c**)*

(89%) Solid, MP 86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57–1.67 (1 H, m), 1.81–1.93 (1 H, m), 2.12–2.18 (1 H, m), 2.58–2.65 (1 H, m), 3.58 (1 H, tt, J = 12.4, 1.6 Hz), 4.17–4.24 (1 H, m), 4.70 (1 H, dd, J = 11.2, 2.0 Hz), 4.78–4.98 (1 H, m), 4.90 (1 H, dd, J = 12.8, 1.6 Hz), 7.42–7.47 (1 H, m), 7.64–7.68 (1 H, m), 7.81 (1 H, d, J = 8.0 Hz), 7.94 (1 H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 18.3 Hz), 39.3 (d, J = 18.3 Hz), 65.7 (d, J = 12.2 Hz), 73.5 (d, J = 12.2 Hz), 88.9 (d, J = 176.1 Hz), 124.5, 128.2, 128.6, 133.9, 137.0, 147.4. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.37 (m, –CF–). IR: 2936, 2858, 1527, 1348, 1158, 1080, 1038, 982, 746, 595 cm^{-1}. Anal. Calcd for $C_{11}H_{12}FNO_3$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.70; H, 5.35; N, 6.26.

*4.1.9. 4-Fluoro-2-(3-nitrophenyl)-tetrahydropyran (**8c**)*

(92%) Solid, MP 94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65–1.76 (1 H, m), 1.80–1.94 (1 H, m), 2.12–2.19 (1 H, m), 2.37–2.43 (1 H, m), 3.59 (1 H, tt, J = 14.4, 2.0 Hz), 4.22–4.28 (1 H, m), 4.44 (1 H, dd, J = 11.6, 2.0 Hz), 4.75–4.95 (1 H, m), 7.53 (1 H, t, J = 8.0 Hz), 7.67 (1 H, d, J = 8.0 Hz), 8.15 (1 H, d, J = 8.0 Hz), 8.25 (1 H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.9 (d, J = 18.3 Hz), 40.6 (d, J = 17.5 Hz), 65.6 (d, J = 12.2 Hz), 76.6 (d, J = 11.4 Hz), 89.0 (d, J = 176.9 Hz), 121.1, 122.9, 129.6, 131.9, 143.7, 148.5. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.71 (d, J = 48.5 Hz, –CF–). IR: 2959, 2858, 1531, 1352, 1160, 1080, 1042, 985, 736, 595 cm^{-1}. Anal. Calcd for $C_{11}H_{12}FNO_3$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.62; H, 5.42; 6.25.

*4.1.10. 4-Fluoro-2-(4-trifluoromethylphenyl)-tetrahydropyran (**9c**)*

(90%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.63–1.75 (m, 1 H), 1.80–1.92 (1 H, m), 2.10–2.20 (1 H, m), 2.32–2.39 (1 H, m), 3.57 (1 H, tt, J = 14.0, 2.0 Hz), 4.20–4.26 (1 H, m), 4.37 (1 H, dd, J = 11.2, 2.0 Hz), 4.73–4.93 (1 H, m), 7.46 (2 H, d, J = 8.0 Hz), 7.61 (2 H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 17.6 Hz), 39.3 (d, J = 17.5 Hz), 65.6 (d, J = 12.2 Hz), 77.0 (d, J = 11.5 Hz), 89.0 (d, J = 177.0 Hz), 124 (q, J = 271.8 Hz), 125.7, 126.2, 130.0 (q, J = 32.1 Hz), 145.5. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.29 (m, –CF–), 99.30 (s, 3F). IR: 2963, 2857, 1622, 1326, 1162, 1126, 1099, 1068, 984, 834, 608 cm^{-1}. Anal. Calcd for $C_{12}H_{12}F_4O$: C, 58.07; H, 4.87. Found: C, 58.12; H, 4.90.

*4.1.11. 4-Fluoro-2-(4-methylsulfanylphenyl)-tetrahydropyran (**10c**)*

(85%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.68–1.77 (1 H, m), 1.80–1.90 (1 H, m), 2.00–2.15 (1 H, m), 2.28–2.34 (1 H, m), 2.45 (3 H, s), 3.57 (1 H, tt, J = 12.4, 2.0 Hz), 4.16–4.22 (1 H, m), 4.28 (1 H, dd, J = 11.2, 2.0 Hz), 4.70–4.90 (1 H, m), 7.23–7.28 (4 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.1, 33.1 (d, J = 17.5 Hz), 40.6 (d, J = 16.8 Hz), 65.6 (d, J = 12.2 Hz), 77.0 (d, J = 12.0 Hz), 89.5 (d, J = 176.1 Hz), 126.6, 126.9, 138.2, 138.4. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.00 (m, –CF–). IR: 2959, 2854, 1496, 1371, 1160, 1082, 1039, 981, 818, 590 cm^{-1}. Anal. Calcd for $C_{12}H_{15}FOS$: C, 63.69; H, 6.68. Found: C, 63.72; H, 6.66.

*4.1.12. 4-Fluoro-2-phenethyl-tetrahydropyran (**11c**)*

(87%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (1 H, p, J = 11.2 Hz), 1.65–1.78 (2 H, m), 1.86–1.95 (1 H, m), 1.98–2.10 (2 H, m), 2.63–2.71 (1 H, m), 2.74–2.82 (1 H, m), 3.20–3.27 (1 H, m), 3.35 (1 H, tt, J = 12.4, 1.6 Hz), 4.00–4.12 (1 H, m), 4.52–4.71 (1 H, m), 7.16–7.20 (2 H, m), 7.26–7.30 (2 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.8, 33.3 (d, J = 17.5 Hz), 37.9, 38.9 (d, J = 16.8 Hz), 65.1 (d, J = 12.2 Hz), 74.8 (d, J = 10.7 Hz), 89.4 (d, J = 174.7 Hz), 126.1, 128.6, 128.7, 142.0. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −7.75 (m, –CF–). IR: 2955, 2853, 1454, 1365, 1164, 1084, 1047, 1009, 994, 700, 571 cm^{-1}. Anal. Calcd for $C_{13}H_{17}FO$: C, 74.97; H, 8.23. Found: C, 74.95; H, 8.27.

*4.1.13. 4-Fluoro-2-(4-nitrophenyl)-6-phenyltetrahydropyran (**12c**)*

(80%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (1 H, p, J = 11.6 Hz), 1.86 (1 H, p, J = 11.6 Hz), 2.46–2.51 (2 H, m), 4.60 (1 H, dd, J = 11.6, 2.0 Hz), 4.70 (1 H, dd, J = 12.0, 2.0 Hz), 4.93–5.14 (1 H, m), 7.31–7.45 (5 H, m), 7.60 (2 H, d, J = 9.2 Hz), 8.23 (2 H, d, J = 9.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.2 (d, J = 12.9 Hz), 40.4 (d, J = 13.7 Hz), 76.4 (d, J = 12.2 Hz), 77.7 d, J = 17.6 Hz), 89.2 (d, J = 178.5 Hz), 123.9, 126.1, 126.8, 128.3, 128.8, 141.0, 147.7, 148.7. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −9.50 (d, J = 48.5 Hz, –CF–). IR: 2926, 2854, 1520, 1347, 1158, 1073, 1054, 852, 698, 586 cm^{-1}. Anal. Calcd for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.80; H, 5.38; N, 4.62.

*4.1.14. 4-(4-Fluoro-tetrahydropyran-2-yl)-benzoic acid methyl ester (**13c**)*

(90%) Solid, MP 80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (1 H, p, J = 11.2 Hz), 1.80–1.92 (1 H, m), 2.11–2.17 (1 H, m), 2.31–2.39 (1 H, m), 3.57 (1 H, dt, J = 12.8, 2.0 Hz), 3.91 (3 H, s), 4.20–4.26 (1 H, m), 4.39 (1 H, dd, J = 11.6, 1.6 Hz), 4.72–4.93 (1 H, m), 7.42 (2 H, d, J = 8.4 Hz), 8.00 (2 H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 18.3 Hz), 40.7 (d, J = 17.5 Hz), 52.3, 65.6 (d, J = 11.4 Hz), 77.0 (d, J = 12.1 Hz), 89.3 (d, J = 176.1 Hz), 125.8, 129.7, 129.9, 146.5, 167.0. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.24 (m, –CF–). IR: 2961, 2858, 1714, 1358, 1279, 1159, 1081, 1033, 960, 772, 590 cm^{-1}. Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.58; H, 6.28.

*4.1.15. Benzenesulfonic acid-4-(4-fluoro-tetrahydropyran-2-yl)-phenyl ester (**14c**)*

(92%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.69 (1 H, p, J = 11.6 Hz), 1.75–1.89 (1 H, m), 2.10–2.14 (1 H, m), 2.27–2.35 (1 H, m), 3.54 (1 H, dt, J = 12.4, 1.6 Hz), 4.16–4.22 (1 H, m), 4.29 (1 H, dd, J = 11.2, 1.6 Hz), 4.69–4.89 (1 H, m), 6.96 (2 H, d, J = 8.8 Hz), 7.27 (2 H, d, J = 8.4 Hz), 7.50–7.54 (2 H, m), 7.64–7.68 (1 H, m), 7.82 (2 H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 16.8 Hz), 40.7 (d, J = 17.6 Hz), 65.6 (d, J = 12.2 Hz), 77.0 (d, J = 18.3 Hz), 89.3 (d, J = 175.4 Hz), 122.6, 127.3, 128.7, 129.4, 134.5, 135.6, 140.6, 149.2. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.36 (m, –CF–). IR: 3079, 2980, 2855, 1705, 1605, 1520, 1346, 1198, 1108, 1058, 854, 700, 529 cm^{-1}. Anal. Calcd for $C_{17}H_{17}FO_4S$: C, 60.70; H, 5.09. Found: C, 60.78; H, 5.12.

*4.1.16. 4-Fluoro-2-hexyl-6-(4-nitrophenyl)-tetrahydropyran (**15c**)*

(80%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (3 H, t, J = 7.2 Hz), 1.18–1.40 (10 H, m), 1.42–1.72 (2 H, m), 2.14–2.20 (1 H, m), 2.20–2.40 (1 H, m), 3.45–3.51 (1 H, m), 4.44(1 H, dd, J = 11.6, 1.6 Hz), 4.72–4.92 (1 H, m), 7.50 (2 H, d, J = 8.4 Hz), 8.17 (2 H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 22.7, 25.5, 29.4, 31.9, 36.0, 38.2 (d, J = 16.8 Hz), 40.4 (d, J = 17.5 Hz), 75.6 (d, J = 12.6 Hz), 76.9 (d, J = 16.2 Hz), 89.3 (d, J = 176.2 Hz), 123.8, 126.6, 147.5, 149.2. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): –8.91 (m, –CF–). IR: 2930, 2857, 1605, 1521, 1348, 1162, 1079, 1014, 854, 750, 602 cm^{-1}. Anal. Calcd for $C_{17}H_{24}FNO_3$: C, 66.00; H, 7.82; N, 4.53. Found: C, 65.97; H, 7.86; N, 4.57.

*4.1.17. 4-(4-Fluoro-6-propyltetrahydropyran-2-yl)-benzoic acid methyl ester (**16c**)*

(80%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.94 (3 H, t, J = 6.8 Hz), 1.30–1.75 (6 H, m), 2.10–2.20 (1 H, m), 2.30–2.40 (1 H, m), 3.40–3.52 (1 H, m), 3.90 (3 H, s), 4.40 (1 H, dd, J = 11.6, 1.6 Hz), 4.72–4.93 (1 H, m), 7.43 (2 H, d, J = 8.4 Hz), 8.01 (2 H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 18.8, 38.2, 38.3 (d, J = 22.1 Hz), 40.4 (d, J = 16.7 Hz), 52.3, 75.3 (d, J = 10.7 Hz), 76.3 (d, J = 11.5 Hz), 88.6 (d, J = 175.4 Hz), 125.9, 129.5, 129.9, 147.0, 167.1. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −8.68 (m, –CF–). IR: 2957, 2872, 1724, 1614, 1435, 1368, 1279, 1160, 1111, 1077, 1019, 856, 769, 705, 603 cm^{-1}. Anal. Calcd for $C_{16}H_{21}FO_3$: C, 68.55; H, 7.55. Found: C, 68.57; H, 7.52.

*4.1.18. 4-Fluoro-2-nonyltetrahydropyran (**17c**)*

(85%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (3 H, t, J = 6.8 Hz), 1.10–1.80 (17 H, m), 1.99–2.11 (2 H, m), 2.17–2.41 (1 H,

m), 3.20–3.30 (1 H, m), 3.31–3.44 (1 H, m), 3.97–4.10 (1 H, m), 4.50–4.80 (1 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.9, 25.6, 29.4, 29.5, 29.6, 29.8, 32.1, 33.3 (d, J = 17.5 Hz), 36.3, 39.0 (d, J = 16.8 Hz), 65.1 (d, J = 11.4 Hz), 76.0 (d, J = 10.7 Hz), 89.6 (d, J = 175.4 Hz). ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −7.54 (m, –CF–). IR: 2926, 2855, 1465, 1367, 1164, 1084, 1010, 869, 722, 609 cm^{-1}. Anal. Calcd for $C_{14}H_{27}FO$: C, 72.99; H, 11.81. Found: C, 72.97; H, 11.85.

*4.1.19. 4-Fluoro-2,2-dimethyl-6-(4-nitrophenyl)-tetrahydropyran (**18**)*

(65%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (3 H, s), 1.41 (3 H, s), 1.47–1.64 (2 H, m), 2.11–2.17 (1 H, m), 2.30-2.40 (1 H, m), 4.71 (1 H, dd, J = 11.6, 1.6 Hz), 4.90–5.11 (1 H, m), 7.55 (2 H, d, J = 8.8 Hz), 8.21 (2 H, d, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.3, 31.9, 40.8 (d, J = 17.6 Hz), 42.7 (d, J = 16.0 Hz), 70.6 (d, J = 11.4 Hz), 74.3 (d, J = 11.4 Hz), 87.7 (d, J = 173.9 Hz), 123.9, 126.9, 147.5, 149.6. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −13.10 (m, –CF–). IR: 2977, 2857, 1602, 1520, 1349, 1191, 1076, 1015, 854, 698, 592 cm^{-1}. Anal. Calcd for $C_{13}H_{16}FNO_3$: C, 61.65; H, 6.37; N, 5.53. Found: C, 61.68; H, 6.41; N, 5.49.

*4.1.20. 4-Fluoro-2-(4-nitrophenyl)-1-oxaspiro [5.5]undecane (**19c**)*

(70%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25–1.39 (2 H, m), 1.41–1.60 (7 H, m), 1.70–1.80 (2 H, m), 1.95–2.00 (1 H, m), 2.15–2.21 (1 H, m), 2.38–2.44 (1 H, m), 4.67 (1 H, dd, J = 12.0, 2.0 Hz), 4.92–5.12 (1 H, m), 7.57 (2 H, d, J = 8.4 Hz), 8.21 (2 H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 21.9, 26.0, 31.3, 40.3, 40.6 (d, J = 17.6 Hz), 42.1 (d, J = 16.0 Hz), 69.0 (d, J = 11.5 Hz), 75.1 (d, J = 11.5 Hz), 87.4 (d, J = 173.1 Hz), 123.8, 126.7, 147.4, 149.9. ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −12.88 (m, –CF–). IR: 2933, 2858, 1601, 1520, 1348, 1174, 1075, 858, 697, 560 cm^{-1}. Anal. Calcd for $C_{16}H_{20}FNO_3$: C, 65.51; H, 6.87; N, 4.78. Found: C, 65.56; H, 6.91; N, 4.75.

*4.1.21. 4-Fluoro-2-1-oxaspiro [5.11]heptadecane (**20c**)*

(50%) Semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23–1.40 (18 H, m), 1.46–1.55 (2 H, m), 1.59–1.77 (2 H, m), 1.80–1.98 (2 H, m), 2.42–2.45 (2 H, m), 3.51–3.58 (1 H, m), 3.78–3.90 (1 H, m), 4.74–4.94 (1 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.7, 19.2, 22.1, 22.6, 22.8, 24.5, 24.8, 26.3, 26.5, 30.1, 32.6 (d, J = 18.3 Hz), 40.4 (d, J = 16.0 Hz), 40.5 (d, J = 9.90 Hz), 58.3 (d, J = 11.0 Hz), 87.8 (d, J = 170.0 Hz). ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −12.83 (m, –CF–). IR: 2930, 2863, 1470, 1362, 1205, 1130, 1074, 943 722, 571 cm^{-1}. Anal. Calcd for $C_{16}H_{29}FO$: C, 74.95; H, 11.40. Found: C, 74.92; H, 11.44.

*4.1.22. 4,13-Difluoro-1,10-dioxa-dispiro[5.2.5.2]hexadecane (**21c**)*

(55%) Solid, MP 113–114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39–1.82 (8 H, m), 1.84–2.00 (6 H, m), 1.95–2.00 (2 H, m), 3.44–3.60 (2 H, m), 3.75–3.86 (2 H, m), 4.75–4.94 (2 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.4, 31.4, 32.4 (d, J = 18.3 Hz), 42.5 (d, J = 17.5 Hz), 57.7 (d, J = 6.9 Hz), 72.4 (d, J = 6.1 Hz), 87.5 (d, J = 11.5 Hz), 87.4 (d, J = 171.6 Hz). ^{19}F NMR ($CDCl_3$–C_6F_6, 376 MHz): −13.17 (m, –CF–). IR: 2935, 2858, 1639, 1379, 1145, 1068, 1028, 825, 729, 537 cm^{-1}. Anal. Calcd for $C_{14}H_{22}F_2O_2$: C, 64.59; H, 8.52. Found: C, 64.62; H, 8.54.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2009.11.002.

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